SUPPLEMENTARY MATERIALS AND METHODS

Bioinformatics analyses of the CDH23 variants

The 1000 Genomes Project, ClinVar, and single-nucleotide polymorphism database are available for assessing the novelty of the variants recognized via clinical whole-exome sequencing. The possible clinical effects of missense compound heterozygous mutations in *CDH23* were evaluated with multiple deleterious prediction tools, including PolyPhen-2, SIFT, PROVEAN, SNAP2, Mutation Taster, and etc.

Here, the features of the human *CDH23* variants were inferred with an array of circulating bioinformatic kits. The native *CDH23* amino acid sequence was obtained from the UniProt database (Q9H251), which was used in the subsequent analyses. The impact of the mutations on protein stability was analyzed by Mutant v2.0, DUET and Maestro Web. The protein secondary structures were analyzed with SOPMA. The isoelectric point (pI) and molecular weight (Mw) of the protein were calculated with ExPASy Compute pI/Mw. ProtScale was used to analyze the hydrophobicity of the polypeptides, and PredyFlexy was used to predict the flexibility profile.

SWISS-MODEL was used in homology modeling for *CDH23* variants, and the best structural templates matching the target sequences were deliberately selected for each candidate domain, including 5tfm.1. A for EC10, 5tfk.1. A for EC19, and 5vvm.1. A for EC21. The molecular dynamics simulation was run upon CHARMm++ 3.2 force field applied to optimize the modeled three dimensional (3D) structures with a protocol in Accelrys Discovery Studio 2.5. The Swiss PDB Viewer was utilized to analyze the 3D structures by calculating (root-mean-square) surface charge distribution and hydrogen bonds to accurately evaluate the effects of mutation on the structural characteristics.